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UNPUBLISHED PRELIMINARY DATA

Subject: Research Progress Report for Research Grant NsG 388

Project title: The Study of the Dynamics of the Cerebral Circulation by Continuous Rheoencephalographic Monitoring

Report Period: June 18, 1964 to December 31, 1964

A. Personnel:

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Studies have been deliberately curtailed to extend remaining funds as close as possible to the project termination date of June 30, 1965. Research efforts have therefore concentrated on those portions of the project which have major bearing on the elucidation of the biophysical basis and clinical applicability of the method and which can conveniently be carried out by the above personnel, most of whom are supported wholly by other funds and who, therefore, are available on a limited basis only.

B. Investigations initiated, suspended, terminated, or completed:

I. General:

All work performed during this report period will be listed; in the absence of specific mention work previously reported "in progress" may be considered suspended or terminated.

II. Clinical:

- 1. The Mount Alto Veteran's Administration Hospital research remained active through October and is presently suspended.
- 2. The rheoencephalography-ballistocardiography study was terminated shortly after initiation.

3. The method of calculation of arterial contributions to the cerebral circulation, previously reported as completed, has been reopened, modified to include an appreciable extra-cranial tracing-component recently discovered, and is presently under theoretical and clinical test.

### III. Basic:

1. The theoretical study of multishelled analogs of the head by field mathematics continues.
2. The transfer impedance study continues. The Schmitt concept has been further modified, extended, and applied to spherical models.
3. Conductivity studies of static and flowing blood have been initiated.
4. A completely general mathematical analysis of the relationship of any plethysmogram to the tissue blood volume variations from which it arises has been initiated and completed. A method of predicting arterial and venous flows based on this analysis has been derived and is under study.
5. A simple Ohm's law analysis of intracranial circulatory events and their effect on the overall impedance of the head has been initiated and completed.

### C. Results and Conclusions:

#### I. General:

As in previous reports minor results will be indicated but no discussed.

### II. Clinical:

#### 1. Tracing analysis:

a. The existence of the appreciable extracranial tracing component reported by Perez-Borja and Meyer has been confirmed and identified by extension of the method of arterial compression previously developed; previous conclusions of this and other investigations that the REG arises solely from intracranial events are therefore erroneous. Approximately 25 cases have been studied and demonstrate the superficial temporal arteries contribute 15-60% of the waveform peak amplitude while the angular and posterior auricular arteries each contribute less than 2% to the tracing. Thus, while the contributions of the latter two arteries are clinically negligible, that of the former is not and must be allowed for in any attempted clinical application.

The previously reported method of arterial component calculation has been successfully extended to include this additional factor; analysis of the above tracings indicates further that the extracranial cross-registry fraction and the extracranial transmidline shunt are usually zero and are always clinically negligible. The previous conclusions regarding the intracranial cross-registry fraction remain valid.

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The above results combined with those previously reported indicate that the problem of identification of individual tracing components is probably complete and can be studied with reasonable rigor. The objection of Perez-Borja and Meyer that REG is useless because of the extracranial "contamination" is erroneous on closer inspection; since the method of occlusions permits the separation of the extracranial and intracranial components their waveforms and amplitudes can be determined and compared both ipsilaterally and contralaterally. Specifically this suggests increased accuracy and refinement in using the method for monitoring normal subjects and the important clinical possibility of localizing cranial circulatory disturbances above or below the carotid bifurcation.

2. The clinical accuracy of the method in the clinic cases continues at its previously reported high level. In one case the presence of pathology was successfully predicted but was lateralized improperly due to the vascularity of the tumor.

Because of the multiplicity of intracranial and extracranial circulatory factors plus those contributed by the method itself the above series of pathological and normal cases should be extended to develop proper criteria for tracing analysis and elucidation of intracranial circulatory mechanisms.

### III. Basic:

1. The above easily demonstrated appreciable extracranial tracing component detected at interelectrode distances greater than 12 cm. where there is no "near field" overlap suggests either there is an appreciable shunting of the current through subcutaneous tissue paths rather than through the intracranial region, or the subcutaneous circulatory changes, despite their small magnitude, are magnified in the "near field" region about the electrodes, or a combination of these mechanisms is operant. The previously reported plots of resistance versus interelectrode distance show a rapid fall in resistance below 8 cm. due to "near field" overlap and associated increased extracranial shunting of current. The above observations suggest the employment of extreme caution in attempting to ascribe an appreciable intracranial component to tracings taken with electrodes placed closer than 7 cm. apart.
2. Detailed consideration of the previously reported proof of Schmitt's transfer impedance concept indicates the previous remarks continue valid; the passive electrical properties of head can be determined by such measurements, provided the measurements are taken in three dimensions, i.e. not only from the surface but at interior points. Since this requires depth electrode studies, which are invalidated by disruption of skull continuity, the method offers only the advantage of determining the impedance properties of the head from voltage mapping alone when current and impedance distributions are unknown.

Since the aim in developing this method is to impedance-map the head without penetrating the scalp various mathematical extensions were considered and discarded until the following formulation was found. The surface geometry of a head can be measured quite precisely; the gross anatomy of the head and brain is known, is tabulated in various stereotaxic atlases, and is reasonably regular and symmetrical. Using the known geometry of anatomical structures one can mathematically assume the head to be made up of subvolumes whose boundaries coincide with known structures each of which might reasonably be assumed to be electrically homogeneous.

The properties of each subvolume need not be similar to those of any other subvolume and are, of course, unknown.

If one next measures the transfer impedance function over the head, imposes the measurements on the above geometrical analog, and solves for the electrical properties of the various subvolumes, one obtains the desired three-dimensional impedance density map of the head from what are essentially two-dimensional surface measurements. Since the electrical properties change markedly with frequency multiple measurements would be necessary.

Since electrical properties change with disease such a map may permit localization of pathology once a sufficient number of normals has been studied.

Once such a map has been obtained for the proper frequencies, surface signals (EEG activity) can be measured and their sources located in three dimensions.

Finally, such a map will enable the prediction of current field distributions, the relative weighting for the various EEG component values, and the conversion of these weighted values to blood volumes and flows.

The accuracy of mapping is limited by the number and size of the assumed subvolumes which are, in turn, limited by the computing capabilities at hand. Present information suggests the number of subvolumes which can be handled will be sufficiently large that major subcortical structures can be separated.

3. The analysis of the multishelled head model has been carried forward sufficiently to determine the computability of the unknown conductivities of the various regions using voltages measured at selected surface points on the model. Unfortunately the equations cannot be programmed.

A simplification involving averaging of voltages measured around circles of latitude was equally not computable, but a further simplification requiring averaging of voltages as above plus along circles of longitude reduces the manipulations to desk calculator simplicity. At present the possibility of applying this simplified method to a prolate spheroid, a better model of the head, is under investigation. When completed, various subjects will be measured to determine the conductivities and di-

electric constants of living scalp, skull, CSF, and "lumped" brain. These values for the various solid tissues are otherwise almost impossible to obtain.

Values obtained by the above two methods should converge as mutual accuracy checks.

4. Recently, electrode designs have been reported which eliminate the "streaming potentials" and motion "artifacts" frequently observed during biological studies. Consideration of their presumed mechanism of function indicates that the apparent conductivity of a homogeneous solution flowing through a standard conductivity cell should rise with increased flow velocity. Several publications report the conductivity of blood rises with increased flow velocity and have been cited against REG analysis based on purely volumetric changes. A study to redetermine blood conductivity at various flow rates is necessary and has been initiated.

As presently planned a conventional conductivity cell for flowing liquids will be modified to include several remote undisturbed electrodes so that both types of measurements can be taken simultaneously on the same flowing liquid.

A coaxial cell is also being designed for the same measurements by pulse analysis methods not only to check the above values by a non-quasi-static method but also to attempt to detect any inductance that may be present in the biological material. The latter is of interest as biological materials apparently have no measurable inductance.

5. A method of preparing rigid homogeneous isotropic spheres of agar-agar gel dimensionally accurate and stable to within 0.001" whose conductivity can be easily varied through a wide range of values has been successfully developed.

Surface voltage plots for currents applied at various electrode position agree well within experimental accuracy with those theoretically predicted and substantiate the previously reported use of these models.

Preliminary results indicate the transfer function method characterizes these conductive volumes extremely well; depth sources can be localized within experimental accuracy. The possibility of characterizing the passive electrical properties of the head by such indirect methods is thus reinforced. Once a subject's head has been so studied the problem of the biophysical origin of the REG tracing components and their relative weighting for conversion to blood volumes can be easily determined. Further, the sources of various EEG signal components can equally well be localized.

6. The validity of the long accepted Munro-Kellie hypothesis of the invariance of the intracranial volume has been challenged on the basis

that the REG tracing indicates an increase in conductivity with systolic arterial inflow. The Munro-Kellie hypothesis requires that blood, having a lower conductivity than CSF, displace CSF with arterial inflow; superficial consideration would then predict a decrease in conductivity at variance with the observed REG events.

If one assumes (for derivational simplicity) the head is a sphere composed of an interior sphere of blood covered with a thin spherical shell of CSF contained in a rigid spherical shell of bone having appropriate openings for fluid shifts, all covered by a final spherical shell of blood, Equation (1) can be derived for the intracranial conductivity change assuming the validity of the Munro-Kellie hypothesis:

$$(1) \quad dL_i = \frac{(\sigma_c + \sigma_b)}{8x_b^2} dV_{B_i} = k_i dV_{B_i}$$

where  $\sigma_c$  and  $\sigma_b$  are the conductivities of CSF and blood,  $x_b$  is the radius of the blood volume expressed as a sphere, and  $dV_{B_i}$  is the change in blood volume.

It should be noted this equation predicts an increase in conductivity despite the CSF displacement.

A similar treatment gives the conductivity changes for the extracranial layer (Equation 2):

$$(2) \quad dL_o = \frac{\sigma_b}{8x_s^2} dV_{B_o} = k_o dV_{B_o}$$

Since these conductances are in parallel the differentials sum (Equation (3)):

$$(3) \quad dL_T = dL_i + dL_o = k_i dV_{B_i} + k_o dV_{B_o}$$

which predicts the observed phenomena and also the already discussed different weighting constants for extracranial and intracranial blood volume changes when expressed as conductance changes.

Shifting the electrodes from diametrical placement closer together varies the weighting constants (as might be expected) but does not change the sign relations.


Changing the geometry to a prolate spheroid, already shown to be a close approximation of the head, does not change the above conclusions, nor does changing the blood volume to volumes of tissue containing a uniform distribution of blood.

7. If one considers that the blood content of any tissue region consists of a time-variable pulsatile flow component arising from variations

in systolic pressure, a constant flow component due to diastolic pressure, and a constant volume representing the tissue blood content at zero pressure, expressions can be easily written for both a plethysmogram recorded by any method and for the blood volume in the corresponding tissue.

Differentiating twice one finds the second derivatives of both expressions are identical. Mathematically, the blood volume and the plethysmogram depend in part on the difference between the arterial inflow and the venous outflow; where the second derivative is zero these flows are constant and equal. Since during the latter portion of systole the arterial pressure falls at a rate governed by the constant capillary resistance, the remainder of the second derivative curve from the zero portion to the onset of the next systole reflects purely venous outflow changes. If these are considered to be symmetrical, i.e., the rise in venous outflow with onset of systolic pressure rise is a mirror image of the fall in venous outflow with systolic pressure fall, one can choose a point on the plethysmographic first derivative curve corresponding to somewhere in the zero portion of the second derivative, consider it and all subsequent events to the next systolic onset to be venous outflow, and construct a curve representing the venous flow function. This latter subtracted from the plethysmographic first derivative gives the arterial flow function. It should be noted that this result varies slightly but significantly from the currently accepted concept that venous outflow is constant; it predicts the venous outflow rises with rising systolic pressure to a higher level which then remains reasonably constant throughout the pulse until no longer sustained by the falling systolic pressure.

Review of the literature indicates no studies have been performed where instantaneous arterial and venous flows and plethysmograms have been simultaneously determined. Such studies are planned following the conclusion of the resistivity vs. blood flow studies.

  
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